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Original Article

Association between obstructive sleep apnea severity and glymphatic-related DTI-ALPS alterations in newly diagnosed, Drug-Naïve Alzheimer's disease

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is highly prevalent in Alzheimer's disease (AD) patients and is associated with cognitive decline. However, the mechanisms linking OSA to Alzheimer's pathophysiology, especially regarding glymphatic function, remain unclear. This study investigated the relationship between OSA severity and glymphatic-related diffusion abnormalities, as assessed by the DTI-ALPS index, in newly diagnosed, drug-naïve AD patients.

Methods: A total of 162 newly diagnosed, drug-naïve AD patients and 98 healthy controls were enrolled. Polysomnography (PSG) was used to assess OSA severity and sleep parameters, while diffusion tensor imaging along the perivascular space (DTI-ALPS) was employed to measure glymphatic function. Correlation analyses, multivariable regression models with interaction terms, and sensitivity analyses were performed to explore the relationship between OSA and glymphatic dysfunction, and whether this relationship was specific to AD.

Results: In AD patients, greater OSA severity was associated with lower ALPS-index values, including AHI (rho = −0.38, $P < 0.001$) and ODI (rho = −0.35, $P < 0.001$), whereas these associations were not observed in healthy controls. Lower ALPS-index values were also associated with more fragmented sleep, including higher N1 proportion and arousal index, and with reduced REM sleep. Clinically, the ALPS-index was positively correlated with better cognitive performance on MMSE (rho = 0.28, $P = 0.001$) and MoCA (rho = 0.31, $P < 0.001$), and negatively correlated with greater cognitive impairment on ADAS-Cog (rho = −0.34, $P < 0.001$).

Conclusion: Glymphatic dysfunction is related to OSA severity in de novo AD but not in Healthy controls. The study demonstrated that OSA may contribute to neurodegeneration via glymphatic impairment in AD.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and is characterized by progressive cognitive decline accompanied by widespread dysfunction of the central nervous system [1–3]. Sleep disturbances are highly prevalent in individuals with AD and commonly manifest as increased sleep fragmentation, reduced slow-wave and rapid eye movement (REM) sleep, and decreased sleep efficiency[4,5]. Obstructive sleep apnea (OSA), a frequent sleep disorder in the aging population, appears to be even more common among patients with AD[6–9]. Accumulating clinical evidence suggests that OSA may be associated with cognitive impairment, an increased risk of developing AD, and abnormalities in neuroimaging findings as well as fluid-based biomarkers [10–14]. Despite these observations, the central physiological pathways linking sleep disorders to AD remain poorly understood [15–17].

The glymphatic system plays a crucial role in the exchange of cerebrospinal fluid (CSF) and brain interstitial fluid, facilitating the clearance of metabolic waste products, including proteins such as β-amyloid and tau [18–20]. Previous studies had found that glymphatic function is enhanced during sleep, particularly during slow-wave sleep [21–26]. On the other hand, sleep deprivation or fragmented sleep has been shown to significantly impair this system's function [27–30]. In AD research, impaired glymphatic function is increasingly recognized as a potential

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contributor to the accumulation of β-amyloid plaques and tau tangles, two hallmark pathological features of AD[18,20,31,32]. However, while these findings are promising, direct and quantifiable human imaging evidence linking sleep disruption, glymphatic dysfunction, and AD remains limited[31,33,34].

Diffusion tensor imaging along the perivascular space (DTI-ALPS) is a non-invasive MRI-based technique that has been developed to assess glymphatic function in vivo [35–40]. This method has been applied to study glymphatic function in various contexts, including normal aging, Parkinson's disease, and specific neurodegenerative diseases [41–46]. Previous studies have shown that the ALPS-index decreases with age and is reduced in certain neurological disorders, which suggests a role of glymphatic dysfunction in the pathophysiology of these conditions [47, 48]. However, studies specifically examining DTI-ALPS in Alzheimer's disease patients remain limited, and few studies have systematically integrated polysomnographic sleep parameters with ALPS indices to investigate the combined effects of sleep fragmentation and glymphatic dysfunction in AD. Taken together, there is a notable gap in the literature, especially regarding studies that simultaneously combine OSA severity, sleep architecture, and glymphatic function in human subjects with AD.

Despite the growing body of evidence linking sleep disturbances with cognitive decline [18,24,49], it remains unclear whether OSA and sleep architecture disruptions are directly associated with impaired glymphatic function in AD. The primary aim of this study was to investigate whether OSA severity and sleep architecture disturbances are associated with impaired glymphatic function (DTI-ALPS) in newly diagnosed, drug-naïve AD patients. Additionally, we sought to compare this relationship between AD patients and healthy controls, examining whether it is specific to AD. By integrating overnight polysomnography (PSG) and DTI-ALPS imaging, this study attempts to provide systematic human evidence for the relationship between sleep disorders, glymphatic dysfunction, and AD.

2. Methods

2.1. Study design and participants

This study employed a cross-sectional, case–control design to investigate the association between sleep-related characteristics and glymphatic function. Participants included newly diagnosed, drug-naïve patients with AD and age-matched healthy controls, allowing comparisons under conditions minimally influenced by pharmacological treatment or disease duration.

A total of 162 patients with Alzheimer's disease and 98 healthy control participants were enrolled. All participants were recruited at The First Affiliated Hospital of Soochow University during the study period through outpatient clinics, inpatient services, and community-based health examinations. Only newly diagnosed patients who had not received anti-dementia medications or other drugs known to substantially affect sleep architecture or central nervous system function were included. Healthy controls were free of cognitive impairment and had no history of major neurological or psychiatric disorders.

The study protocol was approved by the Institutional Ethics Committee of The First Affiliated Hospital of Soochow University, and all procedures were conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants or their legally authorized representatives prior to enrollment.

2.2. Diagnostic criteria and definition of drug-naïve Alzheimer's disease

The diagnosis of Alzheimer's disease was established by experienced neurologists in accordance with the National Institute on Aging–Alzheimer's Association (NIA-AA) clinical criteria [50]. Clinical diagnosis was based on a comprehensive evaluation that included medical history, neurological examination, and standardized cognitive assessments. The CSF analysis or neuroimaging was considered to strengthen diagnostic confidence.

To minimize potential confounding effects related to pharmacological treatment, only newly diagnosed, drug-naïve patients were enrolled. Drug-naïve status was defined as no prior exposure to medications known to influence cognitive function, sleep architecture, or central nervous system physiology, including but not limited to cholinesterase inhibitors, memantine, antipsychotic agents, antidepressants with sedative properties, benzodiazepines, non-benzodiazepine hypnotics, or other centrally acting sedatives.

2.3. Inclusion criteria for healthy controls

Healthy control participants were required to have no history of dementia or mild cognitive impairment, as confirmed by clinical interview and cognitive screening. Individuals with a history of major neurological or psychiatric disorders were not eligible. Control participants were recruited to achieve approximate matching with the Alzheimer's disease group in terms of age and sex distribution, thereby reducing demographic imbalance between groups.

2.4. Exclusion criteria

Participants from both groups were excluded if any of the following conditions were present: 1) Evidence or history of other neurodegenerative disorders, clinically significant cerebrovascular disease, intracranial tumors, or moderate to severe traumatic brain injury; 2) Severe systemic medical conditions, including active malignancy or advanced cardiac, pulmonary, hepatic, or renal failure, which could substantially affect central nervous system function or sleep physiology; 3) Contraindications to MRI or insufficient imaging quality, including excessive motion artifacts or failure to meet predefined quality control criteria for diffusion tensor imaging 4) Inadequate polysomnography recordings, defined as insufficient total recording time or substantial signal loss due to electrode detachment or technical failure. 5) Participants were also excluded if they had received prior formal treatment for obstructive sleep apnea, including continuous positive airway pressure, bilevel positive airway pressure, mandibular advancement devices, upper airway surgery for OSA, or regular oxygen therapy before polysomnography and MRI assessment, because such treatment could affect both PSG-derived OSA severity indices and ALPS-index values.

2.5. Demographic and clinical characteristics

Demographic and clinical characteristics were collected for all participants, including age, sex, years of education, and body mass index (BMI). These variables were used to describe the study population and were considered as potential covariates in subsequent statistical analyses. Information on vascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, smoking status, and alcohol consumption, was obtained through medical records and structured interviews. In addition, a detailed medication history was recorded for all participants. Although patients with Alzheimer's disease were required to be drug-naïve with respect to anti-dementia therapy, the use of antidepressants, anxiolytics, or hypnotic agents was documented separately and considered in sensitivity analyses to account for their potential effects on sleep and central nervous system function. In addition, history of OSA-related treatment, including continuous positive airway pressure, bilevel positive airway pressure, mandibular advancement devices, upper airway surgery, and regular oxygen therapy, was obtained from medical records and structured interviews.

2.6. Cognitive function

To provide a more comprehensive evaluation of cognitive status, additional cognitive instruments were administered in patients with

Alzheimer's disease when available, including the Montreal Cognitive Assessment (MoCA) [51], the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) [52], and the Clinical Dementia Rating (CDR)[53].

2.7. Polysomnography and assessment of sleep-related comorbidities

All participants underwent overnight attended PSG in a dedicated sleep laboratory. Recordings were performed over a standardized time window, typically from 22:00 to 06:00, under controlled environmental conditions. PSG acquisition included continuous monitoring of electroencephalography (EEG), electrooculography (EOG), submental electromyography (EMG), bilateral anterior tibialis EMG, electrocardiography (ECG), nasal airflow, thoracoabdominal respiratory effort, pulse oximetry, body position, and synchronized video recording for behavioral monitoring.

Sleep recordings were scored in accordance with the American Academy of Sleep Medicine (AASM) Scoring Manual (version 2.2, 2015). Sleep stages, respiratory events, arousals, and limb movements were initially scored using a semi-automated system and subsequently reviewed and manually corrected by experienced sleep technologists, who were blinded to participants' clinical diagnosis. Sleep staging was classified into N1, N2, N3, and REM sleep. Arousals were identified according to standard AASM criteria.

Obstructive sleep apnea was defined based on the apnea–hypopnea index (AHI), calculated as the number of apneas and hypopneas per hour of sleep. Apnea was defined as $a \geq 90$ % reduction in airflow lasting at least 10 s, while hypopnea was defined as $a \geq 30$ % reduction in airflow associated with either $a \geq 3$ % oxygen desaturation or an arousal. OSA severity was categorized according to established thresholds. The oxygen desaturation index (ODI) was calculated as the number of oxygen desaturation events per hour of sleep.

The following PSG-derived parameters were extracted for analysis: total sleep time (TST), sleep latency, sleep efficiency, percentage of wake after sleep onset, sleep stage proportions (N1, N2, N3, and REM expressed as percentages of TST), and the arousal index, defined as the number of arousals per hour of sleep. Periodic limb movements of sleep were quantified using the periodic limb movements index (PLMI), expressed as the number of limb movements per hour of sleep.

Sleep-related comorbidities, including insomnia, rapid eye movement sleep behavior disorder, restless legs syndrome, and periodic limb movements of sleep, were identified based on PSG findings and clinical evaluation, and were incorporated into subsequent sensitivity analyses.

2.8. Definition and severity classification of obstructive sleep apnea

OSA was defined according to the apnea–hypopnea index (AHI) derived from overnight polysomnography. Participants with an AHI ≥ 5 events per hour of sleep were considered to have OSA. OSA severity was further categorized based on established clinical thresholds: mild OSA (AHI 5–14.9 events/h), moderate OSA (AHI 15–29.9 events/h), and severe OSA (AHI ≥ 30 events/h). OSA severity was analyzed primarily as a continuous variable to preserve statistical power in correlation and regression analyses. In addition, severity categories were used for descriptive purposes and sensitivity analyses. Specifically, a sensitivity analysis was performed after excluding participants with severe OSA or extreme AHI values, in order to assess whether the observed associations were driven by individuals with marked disease severity.

2.9. Assessment of sleep-related comorbidities

Insomnia symptoms were evaluated using standardized questionnaires or clinical assessment when available. Clinically significant insomnia was defined based on established cutoff scores on the Insomnia Severity Index (ISI) or relevant items from structured clinical interviews. Symptoms of depression and anxiety were assessed using validated screening instruments, including the Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire-9 (PHQ-9), or Generalized Anxiety Disorder-7 (GAD-7), with commonly accepted threshold scores used to indicate clinically relevant symptomatology.

Rapid eye movement sleep behavior disorder (RBD) was identified based on overnight polysomnography combined with synchronized video monitoring. Diagnostic features included the presence of abnormal motor behaviors during REM sleep together with loss of physiological REM-related muscle atonia, in accordance with established criteria. When applicable, clinical diagnosis was further supported by criteria from the International Classification of Sleep Disorders, Third Edition (ICSD-3) [54,55].

Restless legs syndrome (RLS) was diagnosed based on clinical evaluation following the criteria of the International Restless Legs Syndrome Study Group (IRLSSG), including the characteristic urge to move the legs accompanied by uncomfortable sensations, symptom worsening at rest, and relief with movement.

Periodic limb movements of sleep (PLMS) were quantified using polysomnography and expressed as the periodic limb movements index (PLMI), defined as the number of periodic limb movements per hour of sleep. Clinically relevant PLMS was defined as PLMI > 15 events per hour, in accordance with AASM and ICSD-3 criteria.

2.10. MRI acquisition and DTI-ALPS analysis

Magnetic resonance imaging was performed on a 3.0-Tesla MRI system using a 32-channel phased-array head coil. All participants underwent diffusion tensor imaging (DTI) as well as high-resolution structural imaging during the same scanning session. DTI data were acquired using a single-shot echo-planar imaging sequence with the following parameters: repetition time (TR) and echo time (TE) were set according to standard clinical protocols; diffusion weighting was applied along multiple non-collinear directions with a b-value of 1000 s/mm^2, together with non-diffusion-weighted (b0) images. The acquisition employed an isotropic voxel size with contiguous slices covering the whole brain. Phase-encoding directions were recorded to allow for correction of susceptibility-induced distortions when applicable.

High-resolution T1-weighted images were acquired for anatomical reference, spatial normalization, and region-of-interest (ROI) definition. In addition, T2-weighted fluid-attenuated inversion recovery (FLAIR) images were obtained when available to assess white matter hyperintensities, which were rated using the Fazekas scale and incorporated as vascular burden covariates in supplementary analyses.

DTI preprocessing was conducted using standard pipelines and included noise reduction, correction for head motion and eddy-current–induced distortions, and, when applicable, susceptibility distortion correction. Diffusion images were subsequently registered to individual anatomical space and normalized to standard space. All images underwent rigorous quality control, and datasets were excluded if they showed excessive head motion, prominent artifacts, or incomplete brain coverage.

Glymphatic function was assessed using the diffusion tensor imaging–analysis along the perivascular space (DTI-ALPS) method. An automatic atlas-based approach was used to define ROIs within projection fiber areas and association fiber areas in regions adjacent to the lateral ventricles. Directional diffusivities perpendicular to the dominant fiber orientation were extracted to estimate water diffusion along perivascular spaces. The ALPS-index was calculated according to the established formula as the ratio of diffusivities along perivascular directions in projection and association fiber regions.

The index was calculated using the standard method proposed by Taoka et al. [56,57], as:

$$DTI-ALPS = \frac{mean(Dx-proj, Dx-assoc)}{mean(Dy-proj, Dz-assoc)}$$

ALPS-indices were calculated separately for the left and right

hemispheres, and the mean value of both hemispheres was used for subsequent analyses. The automated nature of the ALPS pipeline minimized operator dependence; reliability of the measurements was confirmed in a subset of participants, demonstrating acceptable inter-measurement consistency.

2.11. Statistical analysis

Statistical analyses were performed following a predefined analytical framework aligned with the study objectives and result structure. Continuous variables were first assessed for normality using the Shapiro–Wilk test or, when appropriate, the Kolmogorov–Smirnov test. Normally distributed data are presented as mean ± standard deviation, whereas non-normally distributed variables are reported as median with interquartile range (IQR). Categorical variables are summarized as counts and percentages.

Group comparisons between patients with Alzheimer's disease and healthy controls were conducted using independent-samples t tests for normally distributed continuous variables and Mann–Whitney U tests for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. All tests were two-tailed. When multiple comparisons were performed, correction strategies were applied as specified below.

Associations between the ALPS-index and observed demographic or polysomnographic parameters were examined using Spearman's rank correlation coefficients (rho). Correlation analyses were conducted separately in the Alzheimer's disease and control groups. To account for multiple testing, Bonferroni correction was applied, and statistically significant correlations after correction were highlighted. Where indicated, 95 % confidence intervals for correlation coefficients were estimated using bootstrap resampling.

To evaluate whether the relationship between obstructive sleep apnea severity and glymphatic function differed by disease status, a multivariable linear regression model including an interaction term was constructed. In this primary model, the ALPS-index served as the dependent variable, and independent variables included apnea–hypopnea index (AHI), group (Alzheimer's disease vs. control), the AHI × group interaction, age, sex, sleep efficiency, and periodic limb movements index (PLMI). Regression results are reported as unstandardized coefficients (B), standard errors, standardized beta coefficients, t values, and P values. Model assumptions were evaluated by examining variance inflation factors (VIFs) for multicollinearity, residual distributions for normality and homoscedasticity, and Cook's distance for influential observations.

When a significant interaction effect was identified, post-hoc multivariable regression analyses were performed separately within the Alzheimer's disease group and the control group using the same set of covariates. These analyses were conducted to determine the group in which the association between AHI and ALPS-index was present.

Sensitivity analyses were performed to assess the robustness of the association between AHI and the ALPS-index in patients with Alzheimer's disease. A base model including AHI, age, sex, sleep efficiency, and PLMI was first specified. Sleep-related comorbidities, including insomnia, depression/anxiety, rapid eye movement sleep behavior disorder, restless legs syndrome, and periodic limb movements of sleep, were then added individually and jointly to construct a series of incrementally adjusted models. Changes in the regression coefficients for AHI across models were examined to evaluate potential confounding effects.

Additional robustness analyses were conducted and are reported in the Supplementary Material. First, oxygen desaturation index (ODI) was used as an alternative exposure variable in place of AHI while retaining the same covariate structure. Second, results were re-evaluated using false discovery rate (FDR) correction based on the Benjamini–Hochberg procedure. Third, analyses were repeated after excluding participants with severe obstructive sleep apnea (AHI ≥ 30 events/h) or extreme values. Finally, additional models incorporated measures of Alzheimer's disease severity (Clinical Dementia Rating or ADAS-Cog scores) and vascular burden (white matter hyperintensity burden assessed by Fazekas score) as covariates.

Exploratory analyses were performed to examine the clinical relevance of glymphatic dysfunction. Associations between the ALPS-index and cognitive measures, including MMSE, MoCA, and ADAS-Cog, were assessed using Spearman correlation analyses. In addition, ALPS-index values were compared between patients with mild and moderate Alzheimer's disease using independent-samples t tests or Mann–Whitney U tests, as appropriate.

All statistical analyses were performed using R software and SPSS. Commonly used R packages included stats, psych, sandwich, and ggplot2. A two-sided P value < 0.05 was considered statistically significant unless otherwise specified. For analyses involving multiple comparisons, Bonferroni correction or false discovery rate (FDR) adjustment was applied as appropriate.

3. Results

3.1. Characteristics of study participants

A total of 162 patients with newly diagnosed, drug-naïve Alzheimer's disease (AD) and 98 age-matched healthy controls were included in the analysis. The two groups were comparable in terms of age (68.37 ± 7.92 vs. 68.11 ± 7.58 years, $P = 0.803$), sex distribution (female/male: 74/88 vs. 43/55, $P = 0.893$), years of education (10.73 ± 3.28 vs. 11.41 ± 3.14, $P = 0.112$), and body mass index (24.91 ± 3.21 vs. 25.18 ± 3.09 kg/m^2, $P = 0.541$). As expected, global cognitive performance, assessed by the Mini-Mental State Examination, was significantly lower in the AD group than in controls (22.41 ± 3.27 vs. 28.86 ± 1.31, $P < 0.001$).

With respect to polysomnographic characteristics, total sleep time did not differ significantly between groups (326.84 ± 64.27 vs. 333.19 ± 61.84 min, $P = 0.438$). However, patients with AD exhibited longer sleep latency (27.36 ± 22.41 vs. 21.48 ± 18.62 min, $P = 0.028$), lower sleep efficiency (69.12 ± 15.46 % vs. 74.63 ± 14.28 %, $P = 0.006$), and a higher proportion of wakefulness during the night (27.84 ± 14.92 % vs. 22.63 ± 13.47 %, $P = 0.008$). Sleep architecture analysis further showed a higher percentage of stage N1 sleep (10.47 ± 6.12 % vs. 8.93 ± 5.38 %, $P = 0.041$) and a lower proportion of REM sleep in the AD group (10.63 ± 6.71 % vs. 13.94 ± 6.88 %, $P < 0.001$), whereas the proportions of stage N2 and N3 sleep did not differ significantly between groups.

Importantly, indices of obstructive sleep apnea severity were comparable between AD patients and controls, including the apnea–hypopnea index (18.42 ± 16.27 vs. 19.03 ± 15.84 events/h, $P = 0.781$) and the oxygen desaturation index (16.09 ± 14.88 vs. 15.61 ± 13.97 events/h, $P = 0.807$). The periodic limb movements index was also similar between groups ($P = 0.842$). Nevertheless, the arousal index was modestly but significantly higher in the AD group (15.78 ± 9.64 vs. 13.12 ± 8.41 events/h, $P = 0.024$).

Regarding glymphatic function, the DTI-ALPS index showed a numerical reduction in patients with AD compared with controls (1.26 ± 0.17 vs. 1.29 ± 0.16), although this difference did not reach statistical significance ($P = 0.087$). Other observed parameters did not differ significantly between groups. Detailed demographic, clinical, polysomnographic, and imaging characteristics are summarized in Table 1.

3.2. Associations of DTI-ALPS with observed parameters

In patients with AD, the DTI-ALPS index showed a significant negative correlation with age (rho = −0.34, $P = 0.001$). Importantly, indices of OSA severity were consistently associated with reduced glymphatic function. The ALPS-index was negatively correlated with the AHI (rho = −0.38, $P < 0.001$) and with the ODI (rho = −0.35, $P < 0.001$) (Fig. 1 and Table 2).

Table 1
Comparison of demographic, clinical, polysomnographic parameters and DTI-ALPS index.

Variables	AD ($n = 162$)	Controls ($n = 98$)	P value
Demographic and clinical characteristics			
Age, years	68.37 ± 7.92	68.11 ± 7.58	0.803
Female/Male, n	74 / 88	43 / 55	0.893
Education, years	10.73 ± 3.28	11.41 ± 3.14	0.112
Body mass index, kg/m^2	24.91 ± 3.21	25.18 ± 3.09	0.541
MMSE score	22.41 ± 3.27	28.86 ± 1.31	<0.001
Polysomnographic parameters			
Total sleep time, min	326.84 ± 64.27	333.19 ± 61.84	0.438
Sleep latency, min	27.36 ± 22.41	21.48 ± 18.62	0.028
Sleep efficiency, %	69.12 ± 15.46	74.63 ± 14.28	0.006
Wake, %	27.84 ± 14.92	22.63 ± 13.47	0.008
Stage N1, %	10.47 ± 6.12	8.93 ± 5.38	0.041
Stage N2, %	36.12 ± 12.18	35.48 ± 11.61	0.681
Stage N3, %	14.78 ± 8.94	16.21 ± 8.37	0.207
Stage R (REM), %	10.63 ± 6.71	13.94 ± 6.88	<0.001
Apnea–Hypopnea Index (AHI)	18.42 ± 16.27	19.03 ± 15.84	0.781
Oxygen Desaturation Index (ODI)	16.09 ± 14.88	15.61 ± 13.97	0.807
Periodic limb movements index	9.73 ± 18.41	10.21 ± 19.12	0.842
Arousal index	15.78 ± 9.64	13.12 ± 8.41	0.024
DTI-ALPS			
ALPS-index	1.26 ± 0.17	1.29 ± 0.16	0.087

Values are presented as mean ± standard deviation unless otherwise indicated. Between-group comparisons were performed using the Mann–Whitney U test for continuous variables and the χ^2 test for categorical variables. P values are two-tailed and reported to three decimals; values <0.001 are shown as <0.001. **ALPS**, analysis along the perivascular space; **AHI**, apnea–hypopnea index; **ODI**, oxygen desaturation index; **REM**, rapid-eye-movement sleep; **AD**, Alzheimer's disease.

With respect to sleep architecture and fragmentation, the ALPS-index demonstrated a significant inverse association with the proportion of stage N1 sleep (rho = −0.41, $P < 0.001$) and with the arousal index (rho = −0.33, $P < 0.001$), indicating lower glymphatic function in individuals with more fragmented and superficial sleep. In contrast, the ALPS-index was positively correlated with the proportion of REM sleep (rho = 0.29, $P = 0.001$).

In healthy controls, the ALPS-index was significantly correlated only with age (rho = −0.42, $P < 0.001$). No significant associations were observed between the ALPS-index and measures of OSA severity (AHI or ODI), sleep fragmentation, or sleep stage distribution (all $P > 0.05$)

3.3. Relationship of glymphatic function to sex

Sex-stratified analyses revealed a modest difference in glymphatic function within the AD group. Male patients with Alzheimer's disease exhibited a slightly lower ALPS-index compared with female patients (1.24 ± 0.18 vs. 1.28 ± 0.17, $P = 0.041$). In contrast, no significant sex-related difference in the ALPS-index was observed among healthy controls (1.28 ± 0.16 in males vs. 1.30 ± 0.15 in females, $P = 0.284$). These results are summarized in Table S1.

3.4. Interrelationships among OSA severity and sleep architecture

Higher AHI was significantly associated with lower sleep efficiency (rho = −0.36, $P < 0.001$), a higher proportion of wakefulness during the night (rho = 0.34, $P < 0.001$), and an increased proportion of stage N1 sleep (rho = 0.41, $P < 0.001$). In parallel, AHI was negatively correlated with deeper and consolidated sleep stages, including stage N3 sleep (rho = −0.28, $P = 0.001$) and REM sleep (rho = −0.33, $P < 0.001$) (Table S2).

A broadly similar pattern was observed for the oxygen desaturation index (ODI). Higher ODI was associated with reduced sleep efficiency (rho = −0.39, $P < 0.001$), greater wakefulness (rho = 0.37, $P < 0.001$), and a higher stage N1 ratio (rho = 0.44, $P < 0.001$), as well as lower proportions of stage N3 (rho = −0.31, $P < 0.001$) and REM sleep (rho = −0.36, $P < 0.001$). Notably, while the arousal index was not significantly correlated with AHI (rho = −0.12, $P = 0.129$), it showed a significant positive association with ODI (rho = 0.29, $P = 0.001$).

3.5. Multivariable regression with interaction term between AHI and group

To determine whether the association between OSA severity and glymphatic function differed by disease status, a multivariable linear regression model including an interaction term between AHI and group (AD vs control) was fitted in the full sample. After adjustment for age, sex, sleep efficiency, and periodic limb movements index, age (B = −0.01, standardized β = −0.33, $P < 0.001$) and male sex (B = −0.11, standardized β = −0.29, $P < 0.001$) were independently associated with lower ALPS-index values (Table 3).

The main effect of AHI on the ALPS-index was not significant in the overall sample ($B = 0.00$, $P = 0.401$), nor was the main effect of group (B = −0.02, $P = 0.718$). In contrast, the interaction between AHI and group was statistically significant (B = −0.01, standardized β = −0.41, $P = 0.008$), indicating that the relationship between AHI and glymphatic function differed according to disease status. Sleep efficiency and periodic limb movements index were not significantly associated with the ALPS-index in the fully adjusted model ($P > 0.05$ for both).

3.6. Post-hoc multivariable regression analyses within separate groups

Post-hoc multivariable linear regression analyses were subsequently performed within each group separately to clarify the source of the significant interaction observed in the full-sample model. In patients with Alzheimer's disease, AHI remained independently associated with the ALPS-index after adjustment for age, sex, sleep efficiency, and periodic limb movements index (B = −0.01, standardized β = −0.37, $P < 0.001$). Older age (B = −0.01, standardized β = −0.29, $P = 0.001$) and male sex (B = −0.10, standardized β = −0.24, $P = 0.007$) were also independently associated with lower ALPS-index values, whereas sleep efficiency and periodic limb movements index were not significant predictors ($P > 0.05$ for both) (Table 4).

In contrast, among healthy controls, AHI was not associated with the ALPS-index in the fully adjusted model ($B = 0.00$, $P = 0.634$). In this group, age emerged as the only independent predictor of the ALPS-index (B = −0.01, standardized β = −0.41, $P < 0.001$), while sex, sleep efficiency, and periodic limb movements index showed no significant associations.

3.7. Sensitivity analyses

To evaluate the robustness of the association between OSA severity and glymphatic function, a series of sensitivity analyses adjusting for common sleep-related comorbidities were performed in patients with Alzheimer's disease. In the base model, which adjusted for age, sex, sleep efficiency, and periodic limb movements index, AHI remained independently associated with a lower ALPS-index (B = −0.01, standardized β = −0.37, $P < 0.001$) (Table 5).

After additional adjustment for individual sleep comorbidities, including insomnia, depression/anxiety, rapid eye movement sleep behavior disorder (RBD), restless legs syndrome (RLS), and periodic limb movements of sleep (PLMS), the association between AHI and the ALPS-index remained statistically significant across all models, although the effect size was modestly attenuated. Specifically, the standardized β

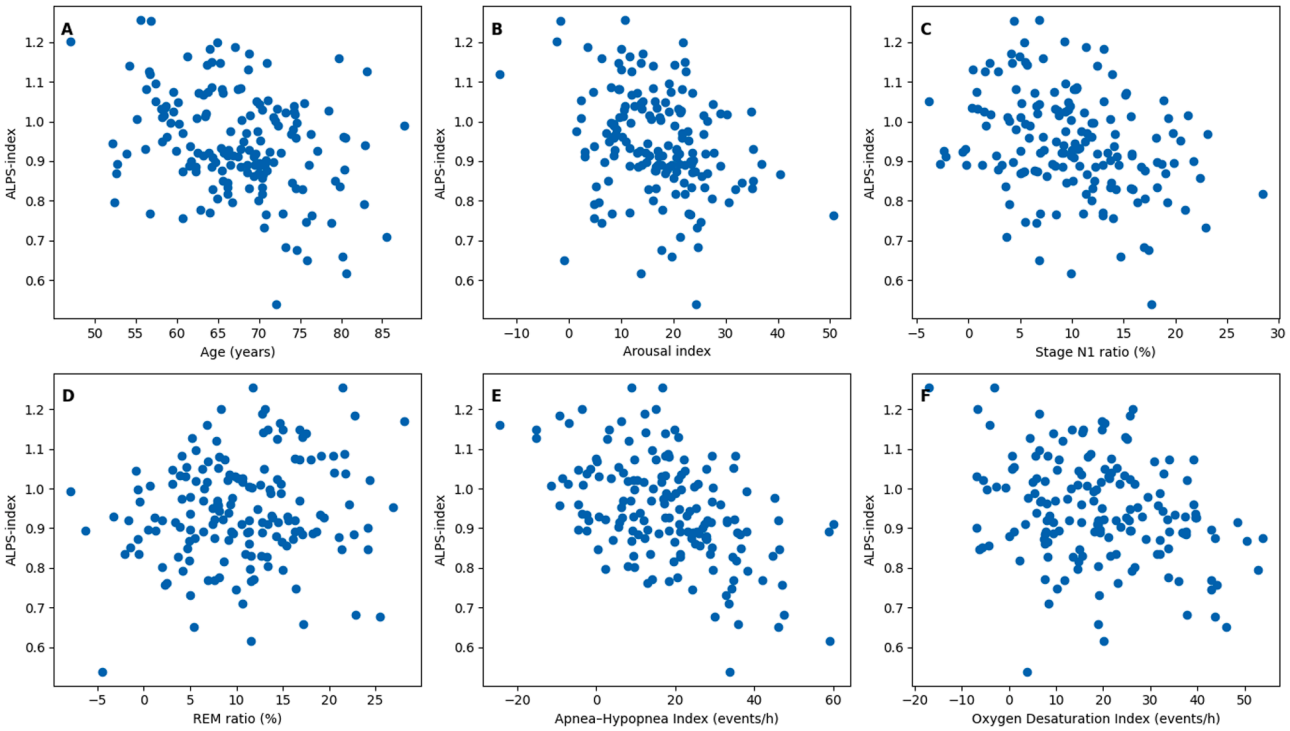

Fig. 1. Correlation plots showing the relationship between the ALPS-index and sleep-related parameters in patients with Alzheimer's disease.
Scatter plots illustrate the associations between the diffusion tensor imaging–analysis along the perivascular space (DTI-ALPS) index and (A) age, (B) arousal index, (C) stage N1 sleep ratio, (D) rapid-eye-movement (REM) sleep ratio, (E) apnea–hypopnea index (AHI), and (F) oxygen desaturation index (ODI). Each dot represents an individual participant. Associations were assessed using Spearman's rank correlation coefficient.

Table 2
Correlations between ALPS-index and observed parameters.

Variables	AD ($n = 162$)			Controls ($n = 98$)		
	rho	P value	95 % CI	rho	P value	95 % CI
Age, years	**−0.34**	**0.001**	−0.46 to −0.19	**−0.42**	**<0.001**	−0.58 to −0.23
Body mass index	−0.11	0.152	−0.26 to 0.05	0.08	0.418	−0.12 to 0.27
Total sleep time	0.06	0.421	−0.09 to 0.20	0.03	0.772	−0.17 to 0.22
Sleep efficiency	0.17	0.029	0.02 to 0.31	0.12	0.248	−0.08 to 0.30
Wake ratio (%)	−0.19	0.014	−0.33 to −0.04	−0.14	0.174	−0.32 to 0.06
Stage N1 ratio (%)	**−0.41**	**<0.001**	−0.54 to −0.26	0.16	0.116	−0.04 to 0.35
Stage N2 ratio (%)	0.09	0.263	−0.06 to 0.24	0.05	0.641	−0.15 to 0.24
Stage N3 ratio (%)	0.11	0.167	−0.04 to 0.26	−0.02	0.872	−0.21 to 0.18
Stage R (REM) ratio (%)	**0.29**	**0.001**	0.14 to 0.43	−0.10	0.332	−0.29 to 0.10
Apnea–Hypopnea Index	**−0.38**	**<0.001**	−0.51 to −0.23	0.07	0.482	−0.13 to 0.26
Oxygen Desaturation Index	**−0.35**	**<0.001**	−0.49 to −0.20	0.05	0.642	−0.15 to 0.24
Periodic limb movements index	−0.14	0.083	−0.29 to 0.02	−0.18	0.091	−0.36 to 0.03
Arousal index	**−0.33**	**<0.001**	−0.47 to −0.18	0.09	0.378	−0.11 to 0.28

Spearman's rank correlation coefficient (rho) was used for correlation analyses.
P values are two-tailed and reported to three decimals; values <0.001 are shown as <0.001. **Bold values indicate statistical significance after Bonferroni correction for multiple comparisons.**
ALPS, analysis along the perivascular space; **REM**, rapid-eye-movement sleep; **AHI**, apnea–hypopnea index; **ODI**, oxygen desaturation index; **CI**, confidence interval; **AD**, Alzheimer's disease.

for AHI ranged from −0.35 ($P < 0.001$) after adjustment for insomnia to −0.31 ($P = 0.004$) after adjustment for PLMS. In the fully adjusted model, which simultaneously accounted for all assessed sleep comorbidities, AHI continued to show an independent association with the ALPS-index (standardized $\beta = -0.29$, $P = 0.006$).

3.8. Robustness analyses

Additional sensitivity analyses were performed to further assess the robustness of the association between OSA severity and glymphatic function in patients with Alzheimer's disease. When ODI was used as an alternative exposure instead of AHI, ODI remained independently associated with a lower ALPS-index after multivariable adjustment (standardized $\beta = -0.34$, $P < 0.001$; Table S3), yielding effect sizes comparable to those observed for AHI. To address potential concerns related to multiple testing, regression results were re-evaluated using false discovery rate (FDR) correction. The associations of the ALPS-index with AHI, age, and sex remained statistically significant after FDR adjustment (FDR-adjusted $P = 0.002$, 0.004, and 0.015, respectively), whereas sleep efficiency and periodic limb movements index remained non-significant (Table S4). Further analyses excluding patients with severe OSA (AHI ≥ 30 events/h) or extreme values produced consistent results. In this restricted sample, AHI continued to show an independent association with the ALPS-index (standardized $\beta = -0.31$, $P = 0.002$),

Table 3
Multivariable regression analysis with interaction term between AHI and group.

Dependent variable: ALPS-index	B	Std. Error	Standardized Beta	t	P value
(Constant)	1.87	0.14	—	13.36	<0.001
Apnea–Hypopnea Index (AHI)	0.00	0.00	0.07	0.84	0.401
Age, years	**−0.01**	0.00	**−0.33**	−4.58	**<0.001**
Sex (male)	**−0.11**	0.03	**−0.29**	−3.67	**<0.001**
Sleep efficiency, %	−0.00	0.00	−0.12	−1.54	0.125
Periodic limb movements index	−0.00	0.00	−0.10	−1.32	0.189
Group (AD vs control)	−0.02	0.05	−0.03	−0.36	0.718
Interaction term: AHI × Group	**−0.01**	0.00	**−0.41**	−2.69	**0.008**

Multivariable linear regression was performed with the ALPS-index as the dependent variable.
The model included apnea–hypopnea index (AHI), age, sex, sleep efficiency, periodic limb movements index (PLMI), group (Alzheimer's disease vs healthy control), and the interaction term between AHI and group. *P* values are two-tailed and reported to three decimals; values <0.001 are shown as <0.001.
ALPS, analysis along the perivascular space; **AHI**, apnea–hypopnea index; **PLMI**, periodic limb movements index; **AD**, Alzheimer's disease.

Table 4
Post-hoc multivariable regression analysis assessing the effect of covariates within the separate groups: AD patients and controls.

Group / Variable	B	Std. Error	Standardized β	P value
A. Alzheimer's disease group ($n = 162$)				
(Constant)	1.92	0.17	—	<0.001
Apnea–Hypopnea Index (AHI)	**−0.01**	0.00	**−0.37**	**<0.001**
Age, years	**−0.01**	0.00	**−0.29**	**0.001**
Sex (male)	**−0.10**	0.04	**−0.24**	**0.007**
Sleep efficiency, %	−0.00	0.00	−0.11	0.188
Periodic limb movements index	−0.00	0.00	−0.09	0.277
B. Healthy control group ($n = 98$)				
(Constant)	1.84	0.21	—	<0.001
Apnea–Hypopnea Index (AHI)	0.00	0.00	0.05	0.634
Age, years	**−0.01**	0.00	**−0.41**	**<0.001**
Sex (male)	−0.04	0.05	−0.09	0.392
Sleep efficiency, %	−0.00	0.00	−0.13	0.230
Periodic limb movements index	−0.00	0.00	−0.12	0.279

Multivariable linear regression analyses were conducted separately in patients with Alzheimer's disease and healthy controls, using the ALPS-index as the dependent variable.
Both models included apnea–hypopnea index (AHI), age, sex, sleep efficiency, and periodic limb movements index (PLMI) as covariates. Regression coefficients (B), standard errors, standardized beta coefficients, and two-tailed P values are reported; P values <0.001 are shown as <0.001.
ALPS, analysis along the perivascular space; AHI, apnea–hypopnea index; PLMI, periodic limb movements index; AD, Alzheimer's disease.

together with age and sex (Table S5). Finally, additional adjustment for Alzheimer's disease severity and vascular burden, including the Clinical Dementia Rating (CDR) global score and Fazekas score, did not materially alter the association between AHI and the ALPS-index (standardized β = −0.30, $P = 0.003$), while CDR and Fazekas scores themselves were not independently associated with the ALPS-index (Table S6).

3.9. Clinical relevance of glymphatic dysfunction

To explore the potential clinical relevance of glymphatic dysfunction, the relationship between the ALPS-index and cognitive severity was examined in patients with Alzheimer's disease. The ALPS-index showed significant positive correlations with global cognitive performance, as assessed by the MMSE (rho = 0.28, $P = 0.001$) and the MoCA (rho = 0.31, $P < 0.001$). In contrast, the ALPS-index was negatively correlated with cognitive impairment severity, measured by the ADAS-Cog (rho = −0.34, $P < 0.001$). Consistent with these continuous associations, patients with moderate Alzheimer's disease exhibited lower ALPS-index values than those with mild disease (1.22 ± 0.18 vs. 1.30 ± 0.16, $P = 0.004$). Detailed results are presented in Table S7.

Table 5
Effect of sleep comorbidities as potential confounders on the association between AHI and ALPS-index in patients with Alzheimer's disease.

Model	Additional covariates included	B (AHI)	Std. Error	Standardized β	P value
Model 1	Base model†	**−0.01**	0.00	**−0.37**	**<0.001**
Model 2	Model 1 + insomnia	**−0.01**	0.00	**−0.35**	**<0.001**
Model 3	Model 1 + depression/anxiety	**−0.01**	0.00	**−0.34**	**0.001**
Model 4	Model 1 + RBD	**−0.01**	0.00	**−0.33**	**0.002**
Model 5	Model 1 + RLS	**−0.01**	0.00	**−0.32**	**0.003**
Model 6	Model 1 + PLMS	**−0.01**	0.00	**−0.31**	**0.004**
Model 7	Model 1 + all sleep comorbidities‡	**−0.01**	0.00	**−0.29**	**0.006**

Dependent variable: ALPS-index (AD group, $n = 162$).
† Base model included apnea–hypopnea index (AHI), age, sex, sleep efficiency, and periodic limb movements index (PLMI).
‡ All sleep comorbidities included insomnia, depression/anxiety, rapid eye movement sleep behavior disorder (RBD), restless legs syndrome (RLS), and periodic limb movements of sleep (PLMS).
Regression coefficients (B), standard errors, standardized beta coefficients, and two-tailed P values are reported; P values <0.001 are shown as <0.001.
ALPS, analysis along the perivascular space; AHI, apnea–hypopnea index; AD, Alzheimer's disease.

4. Discussion

OSA has been associated with AD, though the underlying mechanisms remain unclear [58,59]. In this study, we found that greater OSA severity, as reflected by AHI and ODI, and more fragmented sleep were associated with lower ALPS-index values in patients with newly diagnosed, drug-naïve AD. Importantly, this relationship was not observed in healthy controls and was statistically supported by the interaction term model. The association remained robust across multiple sensitivity analyses, including adjustment for sleep-related comorbidities, use of ODI as an alternative exposure, multiple-comparison correction, exclusion of severe OSA or extreme values, and additional adjustment for AD severity and vascular burden. Moreover, lower ALPS-index values were associated with poorer cognitive performance. These findings suggest that OSA-related sleep disruption may be linked to glymphatic-related diffusion abnormalities in the context of AD, with a disease-dependent vulnerability pattern.

While evidence links sleep disturbances to cognitive decline, it remains unclear whether OSA and sleep disruptions are directly related to impaired glymphatic function in AD [10,16,60,61]. Additionally, it is uncertain whether this association is specific to AD or a general feature of aging, also seen in healthy elderly individuals. If this relationship is specific to Alzheimer's disease, it would suggest a disease-dependent vulnerability pathway rather than a simple age-related or OSA-induced effect. The lack of clarity in this regard is partly due to several limitations in existing studies, including small sample sizes, failure to systematically assess sleep comorbidities, and lack of interaction terms or stratified analyses to directly examine whether this association is indeed disease-specific.

A key finding in this study is the absence of a significant association between AHI/ODI and the ALPS-index in the healthy control group. In

contrast, these sleep-related parameters were strongly linked to glymphatic dysfunction in AD. This suggests that the relationship between sleep disturbances and glymphatic function may be disease-dependent. Several potential explanations could account for this disease-specific effect. First, structural changes in the AD brain, including alterations in white matter integrity, perivascular space dilation, and astrocyte activation, may reduce the brain's ability to compensate for sleep-related disruptions in glymphatic function b[62–67]. Second, AD brain tissue may be more vulnerable to the effects of sleep fragmentation and intermittent hypoxia, potentially magnifying the impact of these disturbances on glymphatic clearance [68–70]. Importantly, these findings do not imply that OSA directly "causes" AD. Instead, they highlight that the effects of sleep disturbances, particularly OSA, may be amplified in the context of underlying AD pathology.

Previous studies have consistently shown that slow-wave sleep and REM sleep are closely linked to metabolic clearance and cerebrospinal fluid dynamics, with disruptions in these sleep stages potentially affecting glymphatic function [34,71–75]. Fragmented sleep, in particular, has been identified as a factor detrimental to glymphatic flow, likely hindering the efficient clearance of waste products from the brain [71,74,76]. In this study, we found that the N1 sleep ratio and the arousal index were negatively correlated with the ALPS-index, while the REM sleep ratio was positively correlated with the ALPS-index. These findings align with previous work suggesting the importance of sleep stages in glymphatic function [72,73,75], yet they add a new layer by linking these sleep characteristics directly to the DTI-ALPS measure of glymphatic flow. Our study benefits from the use of objective, full-night PSG parameters, which provides more precise and reliable data compared to self-reported sleep measures or short-duration sleep studies. Additionally, we simultaneously assessed OSA severity and sleep architecture, allowing for a comprehensive understanding of how these factors influence glymphatic function. Additionally, our study and previous research is that our human data were obtained from Alzheimer's disease patients, allowing us to explore the disease-specific impact of sleep disturbances on glymphatic dysfunction.

To address potential concerns about the robustness of our findings, a series of sensitivity analyses were conducted. These included the use of ODI as an alternative exposure measure to AHI, applying the FDR for multiple comparison correction, excluding extreme values or participants with severe OSA (AHI $\geq$ 30), and adjusting for the presence of sleep comorbidities, such as insomnia, RBD, RLS, and PLMS. Additionally, Alzheimer's disease severity (as measured by CDR or ADAS-Cog scores) and vascular burden (assessed by white matter hyperintensity and Fazekas scale) were incorporated as covariates. Although the effect sizes for AHI and ODI slightly diminished across these sensitivity models, the direction of the association remained consistent, and the findings continued to be statistically significant. These results provide strong evidence supporting the independence of the observed association between sleep disturbances and glymphatic dysfunction.

The association between the ALPS-index and cognitive measures further supports the clinical relevance of our imaging findings. Higher ALPS-index values were associated with better MMSE and MoCA performance, whereas lower ALPS-index values were associated with higher ADAS-Cog scores and more advanced clinical severity. However, given the cross-sectional design, these findings should not be interpreted as evidence that ALPS-index reduction drives cognitive decline. Rather, they suggest that glymphatic-related diffusion abnormalities may accompany greater cognitive impairment in AD and may serve as a complementary imaging marker for future longitudinal studies.

Several limitations of this study should be considered. First, the cross-sectional design precludes any conclusions about causal relationships or the directionality of the observed associations. While our findings suggest a significant link between sleep disturbances and glymphatic dysfunction in AD, future longitudinal studies are required to confirm these findings and assess causality. Second, DTI-ALPS is an indirect imaging marker and should not be considered equivalent to a direct or comprehensive measurement of glymphatic function. The ALPS-index mainly reflects directionally dependent water diffusion along perivascular regions and therefore captures only one specific aspect of glymphatic-related dynamics. It may also be affected by white matter integrity, vascular burden, head motion, and regional anatomical factors. Therefore, our findings should be interpreted as associations between OSA-related sleep disruption and glymphatic-related diffusion abnormalities, rather than direct evidence of impaired global glymphatic function. Third, single-night PSG recordings may introduce variability in sleep parameters due to night-to-night differences, potentially affecting the reliability of the results. A more comprehensive approach involving multiple nights of sleep recording could provide a more accurate reflection of sleep disturbances in the study population. Finally, the study sample consisted of newly diagnosed, drug-naïve AD patients, limiting the generalizability of our findings to other stages of Alzheimer's disease or patients with more advanced disease. This may restrict the external validity of the study, particularly regarding the clinical applicability of the ALPS-index in broader AD populations.

5. Conclusion

This study demonstrated that in AD patients, OSA severity is significantly associated with impaired glymphatic function. Notably, this relationship was not observed in healthy controls, underscoring its disease-specific nature. For the first time, we have established a link between OSA and glymphatic dysfunction, indicating that OSA may exacerbate the neurodegenerative processes of AD through impaired glymphatic function. Given these findings, we recommend routine screening for OSA in the diagnosis of AD.

Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Medical Ethics Committee of the First Affiliated Hospital of Soochow University, Suzhou, China. Written informed consent was obtained from all participants prior to enrollment.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Consent for publication

Not applicable.

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Informed consent

Written informed consent was obtained from all participants prior to enrollment in the study.

Clinical trial number

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The author(s) declared that Generative AI was not used in the creation of this manuscript.

CRediT authorship contribution statement

Wenxue Zheng: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Yao Zhou:** Writing – review & editing, Methodology, Conceptualization. **Yurui Xia:** Writing – review & editing, Methodology, Conceptualization. **Yiqing Wang:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2026.100597.

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